## REMARKS/ARGUMENTS

Claims 1, 3-14, and 25-35 will be pending the above-identified application with entry of the present response. Claims 17-20, 24, 38-41, and 45-69 have been withdrawn by the Examiner as being directed to a non-elected invention. Claims 2, 15-24 and 36-69 are hereby canceled without prejudice to Applicants' right to prosecute the subject matter encompassed by the claims in a related, co-pending application.

Applicants gratefully acknowledge the Examiner's withdrawal of the rejections under 35 U.S.C. § 112, first and second paragraph, under 35 U.S.C. § 102(a), and under nonstatutory obviousness-type double patenting made in the previous office action.

Specification:

The Examiner has objected to the amendment filed October 2, 2007 under 35 U.S.C. §132(a) alleging that it introduces new matter into the disclosure. In particular, the Examiner has objected to the phrase incorporating the earlier related applications by reference. Applicants respectfully disagree with the objection, but to further expedite prosecution of the present application the phrase "the complete disclosures of which are incorporated herein by reference" has been deleted. Accordingly, Applicants believe that the objection is moot.

Rejections Under 35 U.S.C. §103:

Claims 1, 3, 4, and 25 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Klavinskis *et al.* (*J. Immunol.*, 1996, 157:2521-2527) and either Ahlers *et al.* (*J. Immunol.*, 1997, 158:3947-3958) or Berzofsky *et al.* (WO 94/26785). Applicants acknowledge that this rejection is withdrawn against claims 15, 16, 21, and 23 in view of Applicants' cancellation of claims 15-24.

According to the Examiner, Klavinskis *et al.* teaches rectal and vaginal immunization by administering an SIV peptide antigen covalently linked to cholera toxin B subunit (CTB), which was used as an adjuvant. The Examiner alleges that Klavinskis *et al.*

showed that CTLs isolated from the rectal mucosa were antigen-specific. The Examiner admits that Klavinskis *et al.* does not teach the amino acid sequence depicted as SEQ ID NO:9 or an antigen from HIV-1, or administering the antigen without an adjuvant. However, the Examiner asserts that both Ahlers *et al.* and Berzofsky *et al.* disclose the peptide having the amino acid sequence of SEQ ID NO:9. The Examiner alleges that both references describe the peptide having the amino acid sequence of SEQ ID NO:9 as being derived from HIV-1, as an inducer of cytotoxic T cells, and useful for therapeutic or prophylactic vaccines against HIV.

The Examiner believes that it would have been obvious to one of ordinary skill in the art to modify the method taught by Klavinskis *et al.* to administer the peptide having the amino acid sequence of SEQ ID NO:9 to a subject. The Examiner further believes that one would have been motivated to do so given the suggestion by Klavinskis *et al.* that to prevent dissemination of HIV to the regional lymph nodes, an effective vaccine may need to stimulate CTL in the rectal or genital tract. In addition, the Examiner alleges that given that the rectal route is a recognized major route for HIV transmission and given that there is a recognized need in the art to raise a mucosal immune response at the site of transmission, it would have been obvious to administer an antigen/construct to the rectal mucosa in order to reduce transmission. The Examiner asserts that one also would have been motivated by the teachings of Ahlers *et al.* and Berzofsky *et al.* because the amino acid depicted as SEQ ID NO:9 contains an immunodominant HIV CTL epitope. The Examiner believes that there would have been a reasonable expectation of success given the findings of Klavinskis *et al.* that mucosal or targeted lymph node immunization generates antigen-specific CTL in the rectal and genital mucosa.

The Examiner states that as for the use of adjuvants, Klavinskis *et al.* teaches the use of cholera toxin as an adjuvant. It is further asserted by the Examiner that it is known in the art that immune responses can be induced with or without adjuvants, and thus, it is well within the purview of one of ordinary skill in the vaccine arts to administer an antigen with or without an adjuvant. Thus, the Examiner believes that the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

In response to Applicants prior argument that at most Klavinskis *et al.* might suggest incorporating the amino acid sequence of the peptide designated SEQ ID NO:9 into a virus-like construct, the Examiner asserts that there are many known means for delivering an antigen to a subject or to a mucosal surface, suggesting as examples, naked peptide or nucleic acid, virus-like particles expressing the peptide on the surface, liposomes with the peptide encapsulated within the liposome, antigen conjugates, and the like. Further, according to the Examiner, it is well within the purview of one of ordinary skill in the art to select any one of the known antigen delivery methods (form of antigen) to deliver an antigen to a subject. The Examiner believes that this knowledge combined with the disclosure of Klavinskis *et al.* (rectal immunization produces antigen specific CTL in the rectal mucosa) teach the claimed invention.

Applicants respectfully must disagree with the reasoning and conclusions of the Examiner. Contrary to the Examiner's assertions, Applicants submit that there would not have been a reasonable expectation of success for one of ordinary skill in the art to administer any soluble peptide antigen to induce an antigen specific CTL response with or without adjuvant to the rectal and genital mucosa. To one of ordinary skill in the art, the presently claimed invention would have been unpredictable in view of the state of the art at the time of filing. The Examiner has related "means for delivering an antigen" to the form of the antigen used, such as naked peptide and virus-like particles; however, Applicants submit that the type and level of immune response will vary among the various forms of antigen used. As such, the presently claimed invention would have been unpredictable to one of ordinary skill in the art.

In particular, Klavinskis *et al.* induced a CTL response using particulate antigen. Specifically, Klavinskis *et al* constructed a particulate antigen by fusion of a simian immunodeficiency virus p27 gag peptide with Ty virus-like particles, SIVp27:Ty-VLP. The reference does not provide any suggestion or correlation with the predictability that a soluble antigen, in particular, a soluble peptide antigen would induce any type of immune response, much less an antigen specific CTL response. An antigen presented as a particulate can induce an immune response that is different from that induced by a soluble peptide responses for several reasons. The reasons can include, for example, the antigen being a conformation dependent

epitope that is only formed when combined with a virus particle, rather than in soluble form. Moreover, virus-particles may induce CTL responses simply because of the large size, whereas a soluble, small peptide could induce a response through a different mechanism or not at all. In fact, Klavinskis *et al.* in discussing their results note that "[t]he inefficiency of the mucosal route of immunization may relate in part to potential differences in Ag processing. Delivery of the particular Ag SIVp27:Ty-VLP by the TLN route may access macrophages with the capacity to process exogenous particulate Ags for presentation with MHC class I." (Klavinskis *et al.* page 2526, right column, lines 19-23).

In addition to unpredictable responses from using different ways of delivering an antigen (the form of the antigen), the location of administration of the antigen in the subject can influence whether a CTL response would be induced. Klavinskis *et al.* disclose that the response induced by administration of the SIVp27:Ty-VLP particulate antigen differs depending on whether the antigen is administered intrarectally or by targeted lymph node administration. The passage from Klavinskis *et al.* cited above discusses possible reasons for the differences in the immune response observed between the two routes of administration with the same antigen. Further, as disclosed in the original application in Example 1 on pages 33-34, intrarectal immunization resulted in antigen-specific CTL in the mucosal inductive and effector sites, whereas systemic immunization of the same antigen only resulted in a CTL in the spleen and not the mucosal immune system. In addition, in Example 6 a comparison between intrarectal, intragastic, intranasal, and systemic administration of a soluble peptide antigen is provided. The immune response induced by the administration of the same antigen to various sites resulted in different immune responses. Thus, one of skill in the art would not have been able to reasonably predict or expect successful inducement of an antigen specific CTL response in the rectal mucosa through intrarectal or systemic delivery based on the disclosure of Klavinskis *et al.*

Ahlers *et al.* and Berzofsky *et al.* merely disclose the peptide having the amino acid sequence of SEQ ID NO:9 and that the peptide was derived from HIV-1 as an inducer of cytotoxic T cells when administered systemically and that the peptide could be useful for therapeutic or prophylactic vaccines against HIV. There is no disclosure or suggestion that

administration of a soluble peptide antigen, including the peptide having the amino acid depicted as SEQ ID NO: 9, could be administered to the rectal mucosa to induce an antigen specific CTL response. The skill artisan would recognize that there are a finite, but significant, number of forms for a potential antigen derived from an organism and that the form of antigen could be administered in a finite, but significant, number of locations within the body, but there was no certainty as to the whether an immune response would be induced or if an immune response where induced, the type of response. In particular, whether an antigen specific CTL response would be induced by a soluble peptide upon administration to the rectal mucosa.

As to the use of adjuvants, the Examiner has asserted that Klavinskis *et al.* teaches the use of cholera toxin as an adjuvant, but that it is known in the art that immune responses can be induced with or without adjuvants. Further, the Examiner opines that it is well within the purview of one of ordinary skill in the vaccine arts to administer an antigen with or without an adjuvant. Applicants note that while it may be known in the vaccine art that a composition can be formulated with or without an adjuvant, it is not known with a reasonable expectation of success that an immune response will result upon administration of the composition. Klavinskis *et al.* teach that mucosal adjuvant is essential to elicit a mucosal immune response with their particulate antigen. (Klavinskis *et al.*, page 2522, right column, 24-26). In the present invention adjuvant was not required to induce an antigen specific CTL response against a soluble peptide antigen administered to the rectal mucosa. As such, Applicants do not believe that there was a reasonable expectation for success in inducing an antigen specific CTL response to any soluble peptide, much less the peptide designated by SEQ ID NO:9 based on the disclosure of Klavinskis *et al.*

Thus, in view of the comments above, Applicants submit that claims 1, 3, 4, and 25 are not obvious under 35 U.S.C. § 103(a) as being unpatentable over Klavinskis *et al.* (*J. Immunol.*, 1996, 157:2521-2527) and either Ahlers *et al.* (*J. Immunol.*, 1997, 158:3947-3958) or Berzofsky *et al.* (WO 94/26785) and respectfully request the Examiner to reconsider and withdraw the rejections.

Claims 1, 5-14, and 25-35 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Klavinskis *et al.* (*supra*) and either Ahlers *et al.* (*supra*) or Berzofsky *et al.* (*supra*) as applied to claims 1, 3, 4, and 25 above and further in, view of Kiyono *et al.* (*Adv. Drug Deliv. Rev.*, 1995, 18:23-51). According to the Examiner, the teachings of Klavinskis *et al.* are outlined above. Further, the Examiner admits that Klavinskis *et al.* does not teach administering a cytokine to the subject. However, the Examiner asserts that Ahlers *et al.* teaches, immunizing a subject with the peptide of SEQ ID NO:9 and various cytokines (GM-CSF, IL-2, IL-12, IFNγ or TNF- α). The Examiner further alleges that Ahlers *et al.* found that GM-CSF synergized with IL -12 for CTL induction and that TNF- α also synergized with 1L-12, but by a different mechanism. TNF-α and IL-12 were alleged to induce IFNγ production, thus shifting the response to a Th1 phenotype. The Examiner believes that Ahlers *et al.* suggests that in addition to IL-2, for optimum induction of $CD8^+$ CTL *in vivo* requires a combination of cytokines, including GM-CSF and IL-12 to steer the Th1 response toward Th1 cytokines.

According to the Examiner, it would have been obvious to one of ordinary skill in the art to modify the method taught by Klavinskis *et al.* to also administer cytokines to the subject. The Examiner believes that one would have been motivated to do so given the suggestion by Kiyono *el al.* that Th cell-derived cytokines are essential for the induction of appropriate antigen-specific mucosal immune responses and the teachings of Ahlers *et al.* Further, the Examiner asserts that there would have been a reasonable expectation of success given the findings of Ahlers *et al.* with regard to CTL induction by cytokines, and thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

The Examiner asserts that as stated above, the combination of Klavinskis *et al.*, Berzofsky *et al.* (or Ahlers *et al.*) and Kiyono *et al.* teaches administering the claimed peptide composition with a cytokine. Further, according to the Examiner, there are many known ways to deliver an antigen to a subject or to a mucosal surface, *e.g.*, naked peptide or nucleic acid, virus-like particles expressing the peptide on the surface, liposomes with the peptide enclosed in the

liposome, and the like. The Examiner believes that it is well within the purview of one of ordinary skill in the art to select any one of the known antigen delivery methods. Thus, the Examiner asserts that given the teachings of Klavinskis *et al.* (rectal immunization produces antigen specific CTL in the rectal mucosa) and the finds of Kiyono *et al.* (Th cell-derived cytokines are essential for the induction of appropriate antigen-specific mucosal immune responses) and Ahlers *et al.*, it would have been obvious to one of ordinary skill in the art to also administer cytokines along with the antigen to the subject.

Applicants respectfully disagree with the reasoning and conclusions of the Examiner. Contrary to the Examiner's assertions, Applicants submit that there would not have been a reasonable expectation of success for one of ordinary skill in the art to induce an antigen specific CTL response from administering SEQ ID. NO. 9 with or without adjuvant to the rectal and genital mucosa. Further, to one of ordinary skill in the art, the presently claimed invention would have been unpredictable in view of the state of the art at the time of filing. As above, the type and level of immune response will vary among the various forms of antigen for delivery; thus, the presently claimed invention would have been unpredictable to one of ordinary skill in the art. Klavinskis *et al.* merely teaches that an antigen specific CTL response can be induced by administering a peptide conjugated to a particulate antigen to the rectal mucosa followed by an oral administered booster or to a targeted lymph node. The antigen used was designated SIVp27:Ty-VLP. The reference does not provide any suggestion or disclosure that correlates their results with the predictability that intrarectal administration of a soluble peptide antigen would induce an antigen specific CTL response. A particulate versus soluble antigen can induce different responses for several reasons, such as an antigen may have a conformation dependent epitope that is only formed when combined with a virus particle, rather than in soluble form. Moreover, virus-particles may induce CTL responses simply because of the large size, whereas a soluble, small peptide as disclosed in the presently claimed invention could induce a response through a different mechanism. This lack of predictability is further complicated with addition of cytokines, which can affect the CTL response differently depending on the type of antigen used to induce the response.

In addition to unpredictable responses from using different ways of delivering an antigen (the form of the antigen), the location of administration of the antigen in the subject can influence whether a CTL response would be induced. Klavinskis *et al.* disclose that the response induced by administration of the SIVp27:Ty-VLP particulate antigen differs depending on whether the antigen is administered intrarectally or by targeted lymph node administration. The passage from Klavinskis *et al.* cited above discusses possible reasons for the differences in the immune response observed between the two routes of administration with the same antigen. Further, as disclosed in the original application in Example 1 on pages 33-34, intrarectal immunization resulted in antigen-specific CTL in the mucosal inductive and effector sites, whereas systemic immunization of the same antigen only resulted in a CTL in the spleen and not the mucosal immune system. In addition, in Example 6 a comparison between intrarectal, intragastic, intranasal, and systemic administration of a soluble peptide antigen is provided. The immune response induced by the administration of the same antigen to various sites resulted in different immune responses. Thus, one of skill in the art would not have been able to reasonably predict or expect successful inducement of an antigen specific CTL response in the rectal mucosa through intrarectal or systemic delivery based on the disclosure of Klavinskis *et al.*

Ahlers *et al.* and Berzofsky *et al.*, as above, merely disclose, among others, the peptide having the amino acid sequence of SEQ ID NO:9 and that the peptide was derived from HIV-1 as an inducer of cytotoxic T cells when administered systemically and that the peptide could be useful for therapeutic or prophylactic vaccines against HIV. There is no disclosure or suggestion that administration of a soluble peptide antigen, including the peptide having the amino acid depicted as SEQ ID NO: 9, could be administered to the rectal mucosa to induce an antigen specific CTL response. The skill artisan would recognize that there are a finite, but significant, number of forms for a potential antigen derived from an organism and that the form of antigen could be administered in a finite, but significant, number of locations within the body, but there was no certainty as to the whether an immune response would be induced or if an immune response where induced, the type of response. In particular, whether an antigen specific CTL response would be induced by a soluble peptide upon administration to the rectal mucosa.

Ahlers *et al.* and/or Berzofsky *et al.* when considered alone or in any combination with Klavinskis *et al.* do not disclose or suggest the present invention.

Kiyono *et al.* review work of the Collaborative Mucosal Immunization Research Group for AIDS. In their review an ideal vaccine for the prevention of HIV infection is defined as one that should effect primary protection at the mucosal site of entry and secondary humoral and cell mediated immune protection from systemic spread. In addition, such a vaccine is defined as one that should have ease of administration, distribution and production so that world wide immunization is practical. Several mucosal vaccine delivery systems are also discussed and they include live attenuated bacterial vectors, biodegradable microspheres and DNA. See page 37, right column, section 7.1). Further, each of these systems is described in greater detail, but no disclosure or suggestion can be found relating to soluble peptide antigen, such as the chimeric peptide of SEQ ID NO:9. There is nothing in the disclosure of Kiyono *et al.* or any of the other references cited by the Examiner that address the ability of a small soluble peptide antigen to induce any immune response, much less an antigen specific CTL response on administration to the rectal mucosa. It should be noted that the peptides of the invention, including the peptide having the amino acid sequence depicted as SEQ ID NO:9 induced an antigen specific CTL response when administered to the rectal mucosa without administration of either an adjuvant or a cytokine. The peptide formulated with an adjuvant and/or a cytokine was able to produce an enhanced antigen specific CTL response, but was not required. As such, Kiyono *et al.* when considered alone or in any combination with Klavinskis *et al.*, Ahlers *et al.* and/or Berzofsky *et al.* does not disclose or suggest the present invention.

Thus, in view of the comments above, Applicants submit that claims 1, 5-14, and 25-35 are not unpatentable under 35 U.S.C. § 103(a) over Klavinskis *et al.* (*supra*) and either Ahlers *et al.* or Berzofsky *et al.* as applied to claims 1, 3, 4, and 25 above and further in, view of Kiyono *et al.* The Examiner is therefore respectfully requested to reconsider and withdraw the rejections.

## CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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